An expert update on novel therapeutic targets for hyperphosphatemia in chronic kidney disease: preclinical and clinical innovations

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Abstract: Introduction: The management of hyperphosphatemia in patients with chronic kidney disease (CKD) is complicated, requiring a multidisciplinary approach that includes dietary phosphate restriction, dialysis, and phosphate binders.Areas covered: We describe key players involved in regulating inorganic phosphate homeostasis and their differential role in healthy people and different stages of CKD. The contribution of paracellular and transcellular intestinal absorptive mechanisms are also examined. Finally, we illuminate recent therapeutic approaches for hyperphosphatemia in CKD. We searched PubMed/Medline (up to November 2019) using the following terms: chronic kidney disease, dialysis, diet, hyperphosphatemia, NaPi2b, nicotinamide, phosphate binder, secondary hyperparathyroidism, tenapanor and vascular calcification.Expert opinion: The precise mechanisms regulating intestinal phosphate absorption in humans is not completely understood. However, it is now established that this process involves two independent pathways: a) active transport (i.e. transcellular route, via specific ion transporters) and inactive transport (i.e. paracellular route across tight junctions). Dietary phosphate restriction and phosphate-binder use can lead to an undesirable maladaptive increase in phosphate uptake and promote active phosphate transport by increased expression of the gastrointestinal sodium-dependent phosphate transporter, NaPi2b. Nicotinamide may overcome these limitations through the inhibition of NaPi2b, by improved efficacy and reduced phosphate binder use and better compliance.

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An expert update on novel therapeutic targets for hyperphosphatemia in CKD: preclinical and clinical innovations toward 2020

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Short title: Therapeutic targets for hyperphosphatemia in CKD

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Abstract

Introduction: The management of hyperphosphatemia in patients with chronic kidney disease (CKD) is complicated, requiring a multidisciplinary approach that includes dietary phosphate restriction, dialysis, and phosphate binders. An improvement in our understanding of the underlying mechanisms responsible for phosphate homeostasis has led to the development of novel treatment options.

Areas covered: In this review, we describe key players involved in regulating inorganic phosphate homeostasis and their differential role in healthy people and different stages of CKD. We also examine the contribution of paracellular and transcellular intestinal absorptive mechanisms. Finally, we discuss recent therapeutic approaches for hyperphosphatemia in CKD. We searched PubMed/Medline (up to November 2019) using the following terms: chronic kidney disease, dialysis, diet, hyperphosphatemia, NaPi2b, nicotinamide, phosphate binder, secondary hyperparathyroidism, tenapanor and vascular calcification.

Expert opinion: The precise mechanisms regulating intestinal phosphate absorption in humans is not yet completely understood. However, it is now well established that this process involves two independent pathways: a) active transport (i.e., transcellular route, via specific ion transporters) and inactive transport (i.e., paracellular route across tight junctions). Dietary phosphate restriction and the use of phosphate-binders can lead to an undesirable maladaptive increase in phosphate uptake and promoting of active phosphate transport by increased expression of the gastrointestinal sodium-dependent phosphate transporter, NaPi2b. Nicotinamide may overcome these limitations through the inhibition of NaPi2b, by improved efficacy and reduced phosphate binder use and better compliance. Results from ongoing trials in this setting are eagerly awaited.

Key words: phosphate binder, hyperphosphatemia, chronic kidney disease, secondary hyperparathyroidism, vascular calcification

Article highlights

- In healthy adult people, phosphate homeostasis is maintained by the kidneys through action of parathyroid hormone and fibroblast growth factor-23 on the sodium-dependent phosphate cotransporters NaPi2a/c.
- In progressive kidney disease intestinal absorption and its regulation via vitamin D becomes a critical aspect in phosphate management.
- Passive paracellular transport dominates during normal phosphate availability, while the active sodium-dependent transcellular pathways (NaPi2b) become more important in cases of low phosphate availability (i.e. dietetic or pharmacological phosphate restriction).
- Tenapanor is a small-molecule sodium–hydrogen exchanger 3 inhibitor that represents a new drug candidate with a mode of action that is different from phosphate binders. It has already demonstrated robust phosphate-lowering activity in a short-term phase III study.
- Nicotinamide, a modulator of the intestinal NaPi2b expression, has been evaluated in several clinical studies in recent years. Low amounts of nicotinamide and oral phosphate binders may act synergistically to improve phosphate control in dialysis patients.

1. Introduction

Inorganic phosphorus (present in blood in the form of inorganic phosphate) is a mineral that plays an essential role in cell functions, including energy production, membrane transport and cell signalling. Approximately 80-85 % of phosphate is localised in bone, 15% intracellularly in soft tissues and <1% present in serum [1,2].

In healthy individuals, the balance between dietary phosphate intake and renal phosphate excretion is matched and the flow of phosphate between the skeleton and the extracellular phosphate pool is balanced. In CKD patients, phosphate excretion becomes increasingly dependent on the actions of phosphaturic hormones such as klotho-fibroblast growth factor-23 (FGF-23) and parathyroid hormone (PTH). However, these mechanisms cannot compensate for a continuous decline in GFR, and increased phosphate (hyperphosphatemia) eventually occurs. Hyperphosphatemia is defined as serum phosphate levels of >4.5 mg/dL (>1.46 mmol/L). This clinical condition may even be exacerbated through hormonal dysregulation of bone metabolism as a further consequence of the loss of kidney function. This disturbance in phosphate homeostasis is recognised to be associated with vascular calcification [3], and increased cardiovascular (CV) morbidity and mortality [3–7]. Hence, appropriate phosphate management is critical in patients with CKD. The optimal range for serum phosphate in CKD patients remains controversial. KDOQI guidelines of 2011 suggest between 3.5 and 5.5 mg/dL, whereas subsequent 2009 and 2017 KDIGO guidelines [8,9] suggest levels towards the normal range. However, even though as many as 90% of patients with end-stage renal disease (ESRD) are prescribed phosphate binders, only 30-50% of patients reach guideline recommendations [10–16]. This poor achievement of target levels is thought to be mainly attributed to poor adherence to dietary recommendations and phosphate binders (due to high pill burden, complex intake regimens). Yet, recent advances in our understanding of gastrointestinal phosphate absorption suggest that the efficacy of current

treatment options could additionally be limited by counteracting pathophysiological changes of the phosphate transport machinery in the gastrointestinal tract.

2. The burden of phosphate on CKD outcomes

Hyperphosphatemia is associated with a significant increase in the risk of CV morbidity and mortality, observed in both the general population [17,18] as well as in patients with CKD [19–22]. Actually, in pre-dialysis as well as dialysis patients, the risk of CV-related mortality is 10-20 times higher than that of the age-matched general population [23,24]. Vascular calcifications in patients with CKD are linked to CV-related mortality [3] and consequently, novel surrogate markers that estimate the risk for the development of vascular calcification have recently been developed and tested in CKD patients [25–27].

Over 20 years ago Block and colleagues evaluated the distribution of serum phosphate in two large databases from the United States Renal Data System; the Case Mix Adequacy Study (1990) and the Dialysis Morbidity and Mortality Study Wave 1 (1993) [28]. Patients with a serum phosphate >6.5 mg/dL had a 27% increase in the relative risk (RR) of death compared to those with serum phosphate ranging from 2.4 to 6.5 mg/dL. This increased risk persisted even after considering potential confounders such as coexisting medical conditions, dose of dialysis, nutrition status or noncompliance. A few years later, Block reviewed a nationwide database of >40,000 hemodialysis patients and documented a strong association between higher levels of serum phosphate (>5 mg/dL), and increased risk of death. Later, Kestenbaum et al. 2011, observed that serum phosphate levels of >3.5 mg/dL (1.13 mmol/L) were associated with significant risk of mortality in CKD patients not on dialysis [22]. More recently, a meta-analysis (comprising approximately 200,000 patients) by Hou and colleagues was performed on observational studies to assess whether an association exists between abnormal serum phosphate level and risk of all-cause mortality in patients with ESRD requiring dialysis [29]. Results from this meta-analysis demonstrated that patients with

highest or lowest serum phosphate levels were independently associated with increased risk (39%) of all-cause mortality (hazard risk = 1.39; 95% CI 1.31-1.47).

3. Players in phosphate metabolism: intestine, kidney and bone

3.1 Intestinal phosphate absorption

The mechanism of intestinal phosphate absorption in humans is not yet fully understood. However, it is well established that it involves 2 independent pathways: a) active transport (i.e., transcellular route, via specific ion transporters) and inactive transport (i.e., paracellular route across tight junctions), that mainly works at high phosphate concentrations in the lumen and does not show saturation resembling passive diffusion (Figure 1) [30,31].

The sodium-dependent phosphate cotransporter type 2b (NaPi2b; or SLC34A2) plays a key role in active phosphate absorption in the small intestine. In-vivo studies in mice demonstrated that as much as 50% of phosphate is absorbed through NaPi2b [32–34], pointing towards this cotransporter as an important therapeutic target for the management of hyperphosphatemia.

Recently, Knöpfel et al. 2019 demonstrated that in mouse intestinal segments, intestinal tight junctions were shown to be highly permeable to phosphate and acted as a main route for passive phosphate absorption in the intestine [35]. The results of these studies suggest that when exposed to a normal diet, the paracellular pathway is the dominant route, whereas NaPi2b is required when the gradient across the intestinal epithelium is insufficient for passive diffusion to occur [32,33,35].

These two mechanisms and the regulation of different transporters are clearly dependent upon dietary phosphate exposure where phosphate restriction and calcitriol contribute to the stimulation of NaPi2b mediated phosphate absorption [36].

3.2 Phosphate handling in the kidney in healthy individuals

The kidneys are responsible for the reabsorption of approximately 80% of the inorganic phosphate that is filtered by the glomeruli; 60 to 70% resorption in the proximal tubules and 10 to 20% at distal sites [37]. Within the proximal tubule, phosphate transport from the ultrafiltrate across the proximal tubule epithelium is an energy dependent process that requires sodium [38]. The three renal sodium phosphate cotransporters, NaPi2a, NaPi2c, and PiT2, are all localised on the apical brush border membrane of renal proximal tubule cells and use the energy derived from the transport of sodium down its gradient to move inorganic phosphate from the luminal filtrate into the cell [39]. Mouse knockout experiments have shown that NaPi2a accounts for up to 70% of phosphate transport [40]. In contrast, in humans, genetics of inborn forms of renal phosphate wasting have revealed that NaPi2a and NaPi2c may contribute to phosphate reabsorption to a similar extent [41,42]. The precise role of PiT2 in the regulation of phosphate in humans still remains to be clarified [43]. FGF-23 inhibits NaPi2a and 2c thus inhibiting tubular phosphate reabsorption from the primary urine in the kidneys [44]. Moreover, it reduces renal calcitriol synthesis and thus inhibits intestinal absorption via vitamin D receptor dependent and independent mechanisms.

Apart from FGF-23, parathyroid hormone (PTH) is a major modulator of renal phosphate reabsorption. Rising serum phosphate levels as well as declining levels of calcium and calcitriol stimulates PTH synthesis in the parathyroid gland. PTH reduces NaPi2a expression in the proximal renal tubule cells by the PTH1 receptor via protein kinase C and protein kinase A signalling [45,46].

3.3 Bone phosphate absorption

Since approximately 85% of phosphate in humans is localised in bone and teeth, bone health plays a central role in phosphate homeostasis [47]. Bone metabolism depends on a balance between PTH (parathyroid origin) and calcitriol (renal origin). Bone acts as the main buffer for phosphate and calcium and buffering is achieved by the complementary action of these

two hormones. It is now recognised that one of the ways bone can influence outcomes in CKD is through FGF-23 production. High levels of FGF-23 and phosphate are directly proportional to CV events and survival [48].

Several preclinical studies have explored the mechanisms underlying phosphate regulation in the bone. Osteocytes and osteoblasts in bone produce FGF-23 in response to high dietary phosphate/hyperphosphatemia, although this response is delayed compared to that of the parathyroid glands [49]. In cell culture, phosphate can also be sensed by primary osteoblasts and different bone-derived cells. In rat primary mature osteoblasts, extracellular phosphate has been shown to increase the production of FGF-23 and augment the stimulatory effect of 1,25(OH)2 vitamin D3 (calcitriol) on FGF-23 production [50]. FGF-23 transcription levels are also increased in a dose and time-dependent manner by phosphate in a rat osteoblastic cell line following incubation with calcitriol [51]. It was proposed that this effect was mediated via the NADPH-induced production of reactive oxygen species and mitogen-activated protein (MAPK)/extracellular signal–regulated kinase (ERK) signalling pathway. Although the presence of calcitriol in culture media can potentiate the effect of high phosphate on FGF-23 production [50–52], the effect of phosphate may occur (at least partially) without calcitriol. This hypothesis is based on the fact that that hypophosphatemia and low plasma FGF-23 in mice deficient for the VDR can be normalized by feeding animals a Ca^{2+} and phosphate rich diet [53].

4. Dysregulation of phosphate homeostasis in CKD

In individuals with normal renal function, the kidney is mainly responsible for excretion of excess phosphate (between 3,700 and 6,100 mg per day) and thus substantially contributes to phosphate homeostasis. However, as kidney function deteriorates, the capacity to excrete phosphate also declines. Furthermore, serum phosphate levels do not rise markedly until GFR falls below 30 ml/min/1.73 m^2 [54,55] thanks to a compensatory reduction in tubular

resorption, triggered by increased levels of serum FGF-23, PTH, as well as phosphate [56–58]. However, in stage 4/5 CKD, the kidneys are no longer able to excrete the excess of phosphate absorbed by the intestine and hyperphosphatemia almost always develops in those receiving dialysis [54]. Physiologically, the roles of FGF-23 and PTH are to maintain phosphate balance by stimulating its' excretion via the kidneys. However, a progressive loss of kidney function leads to the increased inability of PTH/FGF23 to enhance fractional phosphate excretion. In parallel, renal calcitriol production decreases, bone malfunction and development of hyperphosphatemia ensue, because compensatory mechanisms cannot correct this imbalance.

Although the precise mechanisms of this dysregulation are still poorly understood, it is recognised that chronic exposure to phosphate (possibly also in parallel with calcium) stimulates the release of FGF-23 from bone [59–61]. Thus, it is possible that partial phosphate toxicity may occur by a concomitant increase in FGF-23, particularly in CKD patients where large rises in FGF-23 levels occur [62]. In vitro and studies in animal models demonstrate that FGF-23 can exert a direct effect on the heart, by inducing left ventricular hypertrophy (LVH) [63] in addition to affecting calcium fluxes in cardiomyocytes [64,65], both effects are independent of the presence of phosphate. These findings support the idea that FGF-23 may participate in inducing consequences of phosphate toxicity, at least on the heart in the CKD setting [66]. Therefore, targeting FGF-23 could have benefits. However, this therapeutic strategy was not successful in an animal model of CKD where neutralisation of FGF-23 increased aortic calcification leading to higher mortality rates compared to controls [67]. In this study, the observed negative effect was attributed to high phosphate levels. Further studies evaluating the effect of FGF-23 neutralization in CKD models with controlled phosphate levels and at different stages of CKD will aid our understanding of the role of FGF-23 in CV disease.

In summary, in healthy individuals, inorganic phosphate homeostasis is controlled by active and passive pathways of intestinal phosphate absorption, bone metabolism and renal excretion, with the latter being modulated by endocrine factors [68].

Since both the kidney and bone now cease to play a role in phosphate homeostasis in CKD, the modulation of intestinal phosphate absorption emerges as a prime target for the treatment of hyperphosphatemia [69].

5. Current options for the management of hyperphosphatemia: dietary and pharmacological phosphate restriction

5.1. Dietary phosphate restriction

Recent KDIGO and KDOQI guidelines suggest that dietary phosphate should be limited (daily phosphate intake restricted to 800 to 1000 mg/day and a daily protein intake, as the major source of dietary phosphate to 1.2 g/kg body weight) for the treatment of hyperphosphatemia in combination with other treatments [9,70,71].

Among the phosphate lowering strategies, dietary phosphate restriction remains widely regarded as an integral component of hyperphosphatemia management [9]. However, this strategy is associated with the risk of collateral protein malnutrition [72].

Since foods high in protein content are also rich in dietary phosphate, dietary phosphate restriction mainly involves a reduction in dietary protein intake. This reduction can lead to malnutrition and protein-energy wasting, which are strong risk factors for increased mortality in patients undergoing maintenance dialysis [73,74].

There are several important considerations when proposing dietary phosphate restriction. First, the bioavailability of phosphate needs to be taken into account and not the phosphate content of food alone. In this regard, the source of food (whether it is vegetable or plant based compared to animal based) is an important issue to consider. While the so called “good”

phosphate sources are mainly derived from plant/vegetable sources, excess "bad" phosphate load from food is found in sources that contain phosphate salt additives (processed meats such as cooked ham, roast breast turkey/chicken), and some beverages.

In general, phosphate bioavailability is considerably lower for plant-derived phosphate (e.g. vegetables), compared to meat sources [75]. This is likely attributed to a lower phosphate: protein ratio and the fact that phosphate derived from vegetables (phytate) is absorbed to a lower extent (<50%). In addition, phosphate salts are frequently used as additives to increase shelf-life, improve taste and texture of food items. Almost all processed foods contain phosphate additives, such as disodium phosphate, monosodium phosphate, and potassium triphosphate, to preserve their colour and shelf lives. What is of particular concern is the fact that this "bad" phosphate (e.g. processed foods) is almost completely absorbed (from 80-100%) in the intestine [76,77], compared to only 30-70% by naturally occurring phosphates (phosphoproteins, phospholipids, phosphate esters) [78]. In Western diets, achieving adequate phosphate restriction is challenging due to the high phosphate content (1-1.6 g/day) [79].

In patients with CKD, it is still unclear as to which extent phosphate absorption is modulated by dietary phosphate. Pre-clinical studies have allowed researchers to advance our understanding on the mechanisms underlying dietary phosphate restriction.

Aniteli and colleagues evaluated whether short term alterations of dietary phosphate could impact levels of hormones involved in phosphate metabolism, expression of sodium-phosphate cotransporters, apoptosis, and the expression of matrix extracellular phosphoglycoprotein in various regions of the small intestine in nephrectomised rats [80]. They observed that after 2 days, serum phosphate, phosphate excreted, serum FGF-23, and PTH were significantly higher and ionized calcium was significantly lower in the high dietary phosphate group compared to the low dietary phosphate group. The expression of NaPi2b and PiT-1/2 were increased in the total jejunum mucosa of the low phosphate diet group compared with the high phosphate diet group.

Collectively, preclinical studies have demonstrated that high phosphate diet appears to be linked to low expression of NaPi2b in the intestine, whereas dietary phosphate restriction leads to strong upregulation of NaPi2b [39,80–83]. Moreover, many patients with advanced stages of CKD develop metabolic acidosis which in turn stimulates the expression and activity of NaPi2b [84].

Few clinical studies have investigated the effect of diet and phosphate additive replacement on hyperphosphatemia [85–87]. A 6-month trial on dialysis patients undertaken in Spain compared intensive dietary intervention with usual dietary recommendations. Phosphate levels were significantly lower (multivariate-adjusted difference 0.93 mg/ dl; 95% CI 0.34 - 1.52; p=0.003) in the experimental group with lower prevalence of hyperphosphatemia vs. controls (49% vs. 82%) [87]. The effect of replacing foods high in phosphate additives with food without additives was evaluated in two randomized trials [85,86]. In the first trial by de Fornasari and Dos Santos Sens, 2017, the intervention group received verbal and written counselling on how to replace processed foods that have phosphorus additives (e.g. long life dairy products such as milk or yoghurts, processed meats such as ham turkey and salami, breads, biscuits, cakes, crackers and beverages such as dark cola, black tea) with foods of similar nutritional value without these additives (e.g. plain yoghurts, minas cheese, home cooked meats, homemade breads, biscuits and cakes, homemade ice tea and apple juice). The control group only received nutritional advice before the study. In the second study, Sullivan and colleagues demonstrated that it was possible to achieve a small but clinically significant reduction in serum phosphorus levels in hemodialysis patients after receiving education on avoiding foods with phosphorus additives when purchasing groceries or visiting fast food restaurants. Both studies observed significant reductions in serum phosphate concentrations and hyperphosphatemia after a period of 3 months [85,86].

In summary, apart from a higher risk of malnutrition, an important limitation of dietary phosphate restriction is associated with a compensatory upregulation of the NaPi2b

expression levels, which in turn enhances active phosphate transport. This maladaptive response potentially limits the efficacy of dietary restriction as a strategy in lowering serum phosphate, as the remaining phosphate from food may be absorbed more efficiently by the transcellular pathway.

5.2 Pharmacological approaches to reduce phosphate burden in ESRD:

Oral phosphate binders represent the mainstay in the treatment of hyperphosphatemia in ESRD patients. They effectively reduce the absorption of dietary phosphate in the gastrointestinal tract through the exchange of the anion phosphate with an active cation (e.g. calcium, lanthanum, magnesium, aluminium, iron) and sevelamer to form a nonabsorbable compound that is subsequently excreted with feces.

In-vivo studies have further developed our understanding of the mechanisms by which phosphate binders may act on phosphate transport processes.

Schiavi et al. 2012, used adenine to induce uremia in both NaPi2b-deficient and wild-type mice [88]. NaPi2b-deficient uremic mice were found to have significantly lower levels of serum phosphate and attenuation of FGF-23 compared with wild-type uremic mice. NaPi2b-deficient mice treated with the phosphate binder sevelamer carbonate were further shown to have decreased phosphate levels. Uremic mice were characterised by high turnover of renal osteodystrophy and sevelamer significantly decreased osteoclasts number and rate of mineral apposition in NaPi2b-deficient mice. However, sevelamer had no effect on bone formation or rate of mineral apposition in wild-type mice while it increased the expression of NaPi2b in the uremic mice. The observation that sevelamer has an impact on osteoclast numbers and mineral apposition only in NaPi2b-deficient mice but not in wild-type animals, supports the idea that inhibition of NaPi2b expression might enhance efficacy of therapies targeting luminal phosphate availability in a combination therapy approach.

More recently, Kaesler and colleagues examined the effect of nicotinamide alone and in combination with magnesium carbonate ($MgCO_3$) in CKD mice (nephrectomised and subjected to a 7-week high-phosphate diet) [89]. While $MgCO_3$ treatment alone was observed to increase intestinal expression of the NaPi2b and Pit-1 and decrease calcification severity, nicotinamide alone increased soft tissue and vascular calcification. Nicotinamide in combination with $MgCO_3$ normalized the increased levels of NaPi2b and Pit-1 expression and decreased calcification severity. As pointed out by the authors of this study, major physiological differences exist between mice and humans with regard to intestinal phosphate transport. In humans, NaPi2b is mainly located in the duodenum and jejunum, whereas in mice it is mainly located in the ileum [90]. The dose of nicotinamide used in this in-vivo study was approximately 6-fold higher compared with clinical trials. For these reasons, caution is needed when extending findings from this study to the clinical situation.

Taken together, findings from Schiavi et al. 2012 and Kaesler et al. 2019 show that in experimental models phosphate binder intake is characterized by a compensatory upregulation of NaPi2b, pointing towards the use of a phosphate binder in combination with a NaPi2b inhibitor.

6. Novel treatment options

In clinical practice, as many as 50% of dialysis patients still present with persistently elevated phosphate levels, despite dietary and pharmacological phosphate restriction [91]. Thus, there is a substantial gap between guideline recommendations and clinical practice. As described above, dietary and pharmacological phosphate restriction are characterized by pathophysiological maladaptations that could facilitate active phosphate absorption across the brush border membrane of the gastrointestinal tract, and thus limit the pharmacological efficacy of these current standard treatment options. Novel drug candidates that target

different elements of the intestinal phosphate transport system are currently under development and may provide further prospects for improved phosphate control.

6.1 Targeting renal phosphate excretion

Renal phosphate reabsorption is mediated to a large extent by the NaPi2a (SLC34A1) phosphate transporter located in the proximal tubule. In analogy to inhibition of renal glucose reabsorption by SGLT2 inhibitors, inhibition of renal phosphate transporters may lower phosphate burden in patients with earlier stages of CKD (i.e. those with sufficient GFR to filter relevant amounts of phosphate). Inhibitors of NaPi2a have been developed by several companies and are in preclinical testing [92,93]. The PF-06869206 inhibitor induced transient phosphaturia in normal mice and mice with 5/6 nephrectomy lowering plasma phosphate levels [94]. The inhibitor is also effective in increasing renal phosphate excretion in mice lacking FGF23 or in the adenine-induced CKD mouse model [95]. Similarly, the BAY767 inhibitor also induced phosphaturia and reduced vascular calcifications in a rat model with blocked FGF23 signalling [93]. Thus, inhibition of renal phosphate reabsorption may be a viable option to lower phosphate in those patients with partly preserved GFR.

6.2 Targeting of paracellular intestinal phosphate absorption

Tenapanor is a minimally absorbed small-molecule inhibitor of the sodium/hydrogen exchanger isoform 3 (NHE3) that was originally designed to inhibit the intestinal absorption of sodium [96]. Actually, tenapanor was shown to be able to reduce extracellular fluid volume, LVH, albuminuria and blood pressure in salt fed nephrectomized rats [96]. In a subsequent in-vivo study, it was shown that tenapanor could reduce the intestinal absorption and urinary excretion of phosphate, while fecal phosphate excretion increased [97]. Recently, the mechanism of tenapanor-mediated inhibition of phosphate intestinal absorption has been characterised and it is thought to be independent of SLC34 and SLC20 cotransporters [98].

The mechanism by which tenapanor reduces gastrointestinal phosphate uptake has been investigated in in vivo studies in rodents and translational experiments with human small intestinal stem cell–derived enteroid monolayers to model ion transport physiology. Tenapanor decreases passive paracellular phosphate absorption due to the modulation of tight junctions. At the same time, tenapanor was shown to be able to exert a modest decrease in NaPi2b expression. Still, the reduction of intestinal phosphate absorption is predominantly based on reduction of passive paracellular phosphate flux, an effect mediated exclusively via on-target NHE3 inhibition. When tenapanor was administered to patients undergoing hemodialysis, the increases of both serum phosphate and FGF-23 were prevented in a dose-dependent manner compared to placebo [99–101]. However, to date, we do not know whether tenapanor offers any added value compared to current standard of care (i.e. phosphate binders). Information is also lacking as to whether tenapanor may also act synergistically when used in combination with phosphate binders.

6.3. Targeting of transcellular intestinal phosphate absorption

6.3.1 NaPi2b inhibitor ASP3325

ASP3325 is a novel small-molecule NaPi2b-specific inhibitor that was demonstrated to be safe and effective in reducing systemic phosphate levels in a rat model of adenine-induced renal failure as well as in normal rats fed a high-phosphate diet [102]. A recent clinical trial by Larsson and colleagues failed to show that ASP3325 can alter urinary or fecal phosphate excretion in normal healthy individuals or reduce serum phosphate levels in ESRD patients [103]. The lack of efficacy of ASP3325 in this trial also contrasts other preclinical studies demonstrating a marked reduction in hyperphosphatemia in different rat models [32,102]. Differences in intestinal phosphate transport between rat and human species may possibly explain the negative clinical findings observed by Larsson and colleagues [103]. A dose ranging trial to assess pharmacokinetics, safety and tolerability of ASP3325 has also been

performed in hemodialysis patients with hyperphosphatemia in Japan (NCT02510274), however results from this trial are not yet available[104].

6.3.2 Pan-transporter inhibitors

EOS789 targets the intestinal NaPi2b phosphate transporter as well as the Pit1 and Pit2 transporters which are also located in the intestine. The role of Pit1 and Pit2 in intestinal phosphate absorption is not fully clarified. In healthy subjects, one week of EOS789 reduced urinary phosphate excretion in a dose-dependent manner, while increasing fecal phosphate content [105,106]. In a small group of patients on hemodialysis, EOS789 decreased intestinal phosphate absorption when given alone or in combination with a phosphate binder. While acute EOS789 appears to be well tolerated, no data are available on the long-term efficacy and safety of this molecule.

6.3.3 Nicotinamide

Mode of action and preclinical evidence

While the exact mode of action still remains to be fully understood, preclinical studies have suggested that nicotinamide reduces hyperphosphatemia in a NaPi2b-dependent manner. Over 20 years ago, Katai et al. 1999 were the first to show that nicotinamide inhibits active intestinal phosphate absorption. Rats were treated with either nicotinamide (4 mmoL/kg) or saline [37]. While the sodium-independent phosphate transporter was unaffected by nicotinamide, the sodium-dependent phosphate transport was reduced two-fold following nicotinamide treatment ($p<0.01$). In additional experiments, poly RNA isolated from the jejunum of animals treated either with saline or nicotinamide was injected into *Xenopus* oocytes, and the sodium-dependent phosphate transport capability was assayed. Oocytes injected with RNA isolated from control animals displayed a two-fold increase in phosphate transport vs. water-injected oocytes. In contrast, the injection of RNA isolated from the

jejunum of nicotinamide-treated animals did not change the sodium-dependent phosphate transport level. This study showed that nicotinamide decreases intestinal sodium-dependent phosphate transport and that nicotinamide lowers the level of functional sodium/phosphate cotransporter mRNA in the rat jejunum.

Eto et al. (2006) later evaluated the effects of nicotinamide (4 mmoL/day for six days) on serum phosphate concentration, intestinal phosphate absorption and urinary phosphate excretion in a rat model of adenine-induced chronic kidney failure [107]. While serum phosphate concentrations strongly increased in control animals, phosphate concentrations in animals treated with nicotinamide remained unchanged. Further experiments using radiolabelled phosphate showed that nicotinamide did not affect urinary excretion but inhibited intestinal absorption. Along these lines NaPi2b-protein expression was reduced in the brush border membrane of the jejunum.

In a third preclinical study, the functional importance of NaPi2b in the context of nicotinamide-mediated inhibition of intestinal phosphate absorption was demonstrated by Sabbagh et al.2009 [32]. Wild-type and NaPi2b-deficient mice were fed with a low phosphate diet for 7 days. Following a subsequent phosphate bolus administration, serum phosphate concentration was shown to be strongly increased in wild-type animals. Instead, in NaPi2b-deficient animals only a moderate increase was observed, leading to significantly lower serum phosphate concentrations compared to wild-type animals. The effect seen in wild-type animals could be restored by a prior treatment with nicotinamide while nicotinamide-pre-treatment had no effect in NaPi2b-deficient animals. These results indicate that nicotinamide is dependent upon functional NaPi2b in order to reduce a hyperphosphatemic response following an acute phosphate bolus administration. Nicotinamide also reduces renal phosphate transport and NaPi2a/c expression in rat models[108,109].

Collectively, findings from these animal studies point towards the possibility that nicotinamide may be useful in predialysis and dialysis patients.

The effect of nicotinamide in predialysis patients

Clinical studies have been undertaken in predialysis patients to examine the efficacy of nicotinamide administered as monotherapy [110] or in combination with a phosphate binder [111].

First, a randomised controlled trial by Malhotra and colleagues evaluated the effect of 1,500 or 2,000 mg/d extended-release niacin (i.e. nicotinic acid, a chemical substance closely related to nicotinamide), as monotherapy vs. placebo on plasma phosphate in 352 patients with CKD stages 3 and 4 [110]. Patients that were assigned to niacin showed a decrease in serum phosphate from 3.4 to 3.3 mg/dL compared with an increase from 3.4 to 3.6 mg/dL in the placebo group. Although statistically significant ($P<0.01$), the relevance was questionable as niacin treatment did not result in changes of the CKD-MBD markers FGF-23, PTH, calcium or vitamin D over a period of 3 years.

The effect of nicotinamide administered alone and in combination with a phosphate binder was also evaluated in predialysis patients. COMBINE was a randomized, placebo controlled trial involving 205 patients with stage 3b/4 CKD and the effect of nicotinamide (750 mg twice daily), lanthanum carbonate (1000 mg thrice daily), or both, versus placebo over 12 months was evaluated [111]. It was observed that neither drug (alone or in combination), reduced serum phosphate or FGF-23 significantly compared to the placebo arm or versus baseline concentrations.

Taken together, results from these clinical studies suggest that nicotinamide administered as monotherapy or combined with a phosphate binder appears to have only a limited impact on mineral and bone disease in predialysis patients.

The effect of nicotinamide as monotherapy in dialysis patients

Takahashi and colleagues were the first to show the phosphate-lowering effect of nicotinamide in hemodialysis patients [112]. Sixty-five hemodialysis patients with a serum phosphate levels >6.0 mg/dL after a 2-week washout of calcium carbonate participated in the study. Nicotinamide was administered for 12 weeks at a starting dose of 500 mg/day and increased by 250 mg/day every 2 weeks until serum phosphate levels were <6.0 mg/dL. A 2-week post-treatment washout period followed the cessation of nicotinamide. The mean serum phosphate concentration was 5.4±1.5 mg/dL at the beginning of the pre-treatment washout phase. During washout of the previous phosphate binder serum phosphate rose to 6.9±1.5 mg/dL and decreased again to 5.4±1.3 mg/dL during the 12-week nicotinamide treatment (P<0.0001). At the end of this treatment phase, the mean daily nicotinamide dose was 1,080±370 mg. Median serum iPTH levels decreased from the maximum 230 (90.8 to 582) pg/mL to 150 (57.6 to 518) pg/mL after the 12-week nicotinamide treatment (P<0.05). More recently, in the NICOREN trial, Lenglet et al. 2017 randomized 100 patients on chronic hemodialysis to either open-label oral nicotinamide (0.5–2 g per day) or open-label sevelamer hydrochloride (3.2–9.6 g per day) for 24 weeks to examine noninferiority and safety. Before randomization, all patients underwent a washout period to remove the previous phosphate binder [113].The mean daily nicotinamide and sevelamer doses were 1,300 mg and 8,600 mg, respectively, at the end of the 24-week randomized treatment period. Both nicotinamide and sevelamer decreased serum phosphate to a similar extent, yielding significantly lower serum levels at week 24 compared to the respective baseline levels (from 2.3±0.5 to 1.7±0.5 mM, p<0.001) for sevelamer-group and for the nicotinamide –group (from 2.1±0.4 to 1.8±0.5 mM, p<0.01). However, non-inferiority was not reached, likely due to the lower number of patients included in the study than planned [113]. iPTH did not notably change in both treatment groups. With respect to FGF23 levels, differential changes of median levels were observed (decrease in sevelamer -group, increase in nicotinamide -group). These data are difficult to interpret due to a considerable number of missing values already at baseline (16% in patient

groups) and different attrition rates. The high discontinuation rate was mainly attributed to the high frequency of adverse events in the nicotinamide group (24%) versus patients in the sevelamer group, (4%, p=0.05). However, patients previously treated with sevelamer were not excluded from the study, suggesting possible selection bias favouring tolerability with sevelamer. In conclusion, the results of these two open-label studies suggest that daily nicotinamide doses of at least 1,000 mg are needed in a monotherapy setting in order to achieve a phosphate reduction comparable to phosphate binders. Thus, nicotinamide alone is most likely not able to provide a clinically relevant benefit compared to standard treatment with phosphate binders.

Use of nicotinamide in combination with phosphate binder in dialysis patients

To address the potential use of nicotinamide in combination with oral phosphate binders, several smaller studies performed in dialysis patients have been undertaken in the last ten years.

Three double-blind placebo-controlled studies have evaluated the effect of nicotinamide administered in combination with phosphate binders (calcium-based, sevelamer, and lanthanum carbonate) in adult dialysis patients. Nicotinamide was tested at daily doses between 500 and 1,500 mg in forced titration regimens. All three studies demonstrated a rapid reduction of the serum phosphate concentration for daily doses of 500 mg. Forced titration was associated with a further reduction of serum phosphate. However, this additional effect was less pronounced than the immediate effect seen at 500 mg per day.

Over 10 years ago, Cheng examined the effect of 8 weeks of nicotinamide (500 to 1500 mg/d) vs. placebo in 33 dialysis patients [114]. Serum phosphate levels decreased significantly from 6.26 to 5.47 mg/dL with nicotinamide but not with placebo (5.85 to 5.98 mg/dL).

A further randomized, double blind, placebo controlled trial also evaluated the effect of nicotinamide to reduce serum phosphate levels in adult peritoneal dialysis patients with

hyperphosphatemia over 8 weeks [18]. Patients were randomized to nicotinamide (250 mg twice daily, with titration to 750 mg twice daily) or placebo. Phosphate binders, active vitamin D, and cinacalcet remained constant for the duration of the study. During the first two weeks (500 mg/d) the mean serum phosphate levels has decreased from 5.9±0.6 mg/dL to 5.1±1.0mg/dL in the nicotinamide-group and remained essentially unaffected in the placebo-group (5.5±0.5 mg/dL at baseline, 5.4±0.7 mg/dL at week 2). At the end of the randomized treatment phase (week 8), serum phosphate levels were 5.2±0.9 mg/dL and 5.9±0.4 mg/dL in the nicotinamide- and placebo-group, respectively, with an absolute difference in change between groups of 1.1 mg/dL (p=0.037).

In a trial conducted in Iran by Shabazian and colleagues, 48 hemodialysis patients with hyperphosphatemia were randomly (1:1) assigned to nicotinamide or placebo [115]. In addition to double-blinded intake of the study medication, patients remained on their prior calcium carbonate dose that was to be kept constant throughout the study period. Nicotinamide was administered at 500 mg/day for 4 weeks and a further four weeks at 1,000 mg/day. In the placebo-group, the mean phosphate levels were 5.8 mg/dL, 6.1 mg/dL, and 5.6 mg/dL at baseline, week 4, and week 8, respectively. No statistically significant overall changes were observed for serum phosphate in this treatment group. In the nicotinamide group, the mean phosphate levels rapidly decreased from 5.9±0.58 mg/dL to 4.77±1.43 mg/dl in week 4 (p=0.002 compared to baseline) and only slightly decreased further to 4.66±1.06 mg/dL in week 8 (p=0.000 compared to baseline, not significant compared to week 4). In contrast, the authors reported an apparent dose-dependent reduction of the mean platelet count from 216.5±64.8/nL at baseline to 192.3±65.6/nL at week 4 (not significant) and 168.8±57.0/nL at week 8 (p<0.001). Between-subjects repeated measures analysis of variance was also applied to compare changes in variables for the three time points in the nicotinamide vs. placebo group. Statistically significant differences were observed between the placebo and

nicotinamide groups respectively for phosphorus (5.65 vs. 4.66 mg/dL at 8 weeks, ANOVA; p=0.001).

The use of nicotinamide in combination with phosphate binder has also been evaluated in a pediatric population [116]. In children undergoing hemodialysis, nicotinamide (100 mg two or three times daily) plus calcium-based phosphate binders, or calcium-based phosphate binders alone was evaluated over the course of 6 months. Serum phosphate decreased from 6.9±1.6 mg/dL at baseline to 5.1±0.9 mg/dL at month 6 ($p<0.0001$) in the group receiving nicotinamide and phosphate binders, and statistically significant increase was observed in those receiving phosphate binders alone (baseline, 7.7±1.9 mg/ dL; month 6, 8.1±1.4 mg/dL; $p<0.0001$; between-group comparison, $p=0.001$).

Taken together, these studies indicate that the addition of low doses of nicotinamide (e.g. 500 mg/d) to oral phosphate binders may be a promising future option to improve phosphate control in dialysis patients. Importantly, in this setting the risk for apparent dose-dependent side effects (e.g. gastrointestinal disturbances, reduction of platelet numbers) should be considerably lower compared to a monotherapy with daily doses of 1,000 mg and higher.

7. Conclusion

Dietary phosphate restriction and use of phosphate binders represent the main treatment strategies for hyperphosphatemia in ESRD patients. Growing evidence from animal experiments suggests that these current treatment options may be associated with maladaptive responses of the intestinal phosphate transport machinery that could add to clinically insufficient phosphate control in many patients. Tenapanor, a small-molecule NHE3 inhibitor, represents a new drug candidate with a mode of action that is distinct from phosphate binders and it has already demonstrated robust phosphate lowering activity in a short-term phase III study [100]. Nicotinamide, a modulator of the intestinal NaPi2b expression, has been evaluated in several clinical studies in recent years. Considering all available data, low

amounts of nicotinamide and oral phosphate binders may act synergistically to improve phosphate control in dialysis patients.

8. Expert opinion

Serum phosphate levels remain elevated in approximately half of dialysis patients even after they have undergone dietary and/or pharmacological phosphate restriction. Therefore, a substantial gap still exists between targets specified in guideline recommendations and what is seen in daily clinical practice. A better understanding of the molecular mechanisms involved in phosphate transport and its regulation will allow the development of novel therapeutic agents that can be used to manage hyperphosphatemia in the CKD setting. To date, it is recognised that in addition to active transport, the intestine is also known to absorb luminal phosphate through the passive pathway. However, although this mechanism was proposed over 50 years ago in in-vivo studies, its molecular identity still remains to be fully elucidated (Figure 1). Actually, the vast majority of information available on the potential mechanisms that occur in the intestine is limited to the active component. Current therapeutic options to manage hyperphosphatemia in CKD patients (dietary phosphate restriction as well as phosphate binders), aimed to decrease the uptake of dietary phosphate across the intestinal epithelia, are still suboptimal therapies. Therefore, it is paramount that an extensive molecular characterization of the mechanisms regulating phosphate intestinal absorption in CKD is achieved. We have identified several unmet needs that still remain to be addressed in hyperphosphatemia (Box 1).

One of the main weaknesses of phosphate binders is the fact that their efficacy can be greatly hampered by a lack of adherence [117,118]. This is likely attributed to the high burden of side effects experienced and number of pills consumed in these patients [119]. This is a real concern, since reported rates of non-adherent patients to phosphate binders on average are close to 50% [118,120].

High-quality evidence for the long-term benefits of lanthanum or iron-based binders compared vs. placebo or calcium-based treatment is not yet available from current research. The 2017 LANDMARK trial comparing lanthanum carbonate vs. calcium carbonate among 2309 patients should soon have results and may provide a clearer idea of the effects of lanthanum carbonate in individuals with ESRD on dialysis [121].

In dialysis patients, the "add-on" approach using nicotinamide in combination with phosphate binders and/or phosphate dietary restriction, may be attractive, particularly in patients where dietary restriction and/or phosphate binder therapies alone do not achieve normal phosphate levels. In these patients, management of phosphate concentration and timing of phosphate exposure would favour the combined use of a phosphate binder and phosphate transport inhibitor [122].

Ketteler and colleagues recently evaluated the pharmacokinetic characteristics and short-term tolerability of a novel modified release formulation of nicotinamide (NoPhos) at a dose range between 250 and 1,000 mg) for once daily oral route administration [123]. The authors concluded that NoPhos offers advantageous pharmacological properties compared to immediate release formulations and at the same time ensures a solid phosphate lowering activity after once daily intake. This novel modified release preparation NoPhos represents a novel therapeutic option for haemodialysis patients with hyperphosphatemia.

Data derived from long-term trials for NoPhos as add-on to phosphate binders are also currently unavailable. Results from a phase III multicenter study (EudraCT Nr.: 2013-000488-95) evaluating the therapeutic effect of nicotinamide as add-on approach to phosphate binder in more than 700 hemodialysis patients are eagerly awaited. To date, long-term trials in larger patient cohorts are still needed for tenapanor as it is unclear whether tenapanor can provide an improvement in phosphate control compared to phosphate binders [124].

One of the difficulties encountered in clinical trials examining the effect of phosphate binders, is the fact that often patients in these studies have multiple comorbidities. This frequently

leads to difficulty in trials aiming to observe a reduction in phosphate. Due to the link between hyperphosphatemia and vascular calcification [3], researchers have developed an in vitro blood test that provides a propensity score to extra-skeletal calcification. The test, named maturation time (T50) measures calciprotein particles (CPP) in serum and is based on the difference in timing of the change of calcium phosphate–containing primary CPP to hydroxyapatite–containing secondary CPP.

High serum calcification propensity (i.e., reduced serum T50), defined as the overall tendency to calcify, is associated with the progressive aortic stiffening, a predictor of poor survival. This biomarker has now been tested in a cohort of cohort of 184 patients with stage 3/4 CKD. Baseline T50 was found to be independently associated with aortic pulse wave velocity in all randomized patients, while in about 50% of CKD patients, progressive aortic stiffening was associated to T50 after 30 months of follow-up. Furthermore, the lowest T50 was closely dependent on serum phosphate levels and serum fetuin-A levels [26]. Although few studies have been undertaken to date examining the use of T50 as a surrogate marker of vascular calcification, this biomarker warrants further investigation as a pre-specified endpoint in trials examining benefit of potential treatment approaches in patients with hyperphosphatemia.

Due to limitations in existing studies and a lack of evidence for specific clinical questions, further studies will hopefully yield stronger evidence on the effects of different phosphate binders in CKD, facilitating improved therapeutic management of these difficult to treat patients.

9. Literature search

We searched PubMed/Medline and clinical trials.gov (up to November 2019) for published and unpublished studies using the following terms: chronic kidney disease, dialysis, diet, hyperphosphatemia, NaPi2b, nicotinamide, phosphate binder, secondary hyperparathyroidism, tenapanor and vascular calcification. Studies were excluded that were not published English,

German or Italian language, in addition to hand selected case studies; abstracts; letters and reviews. Duplicate articles, including articles that were not related or not relevant to hyperphosphatemia or the topic discussed, were also removed.

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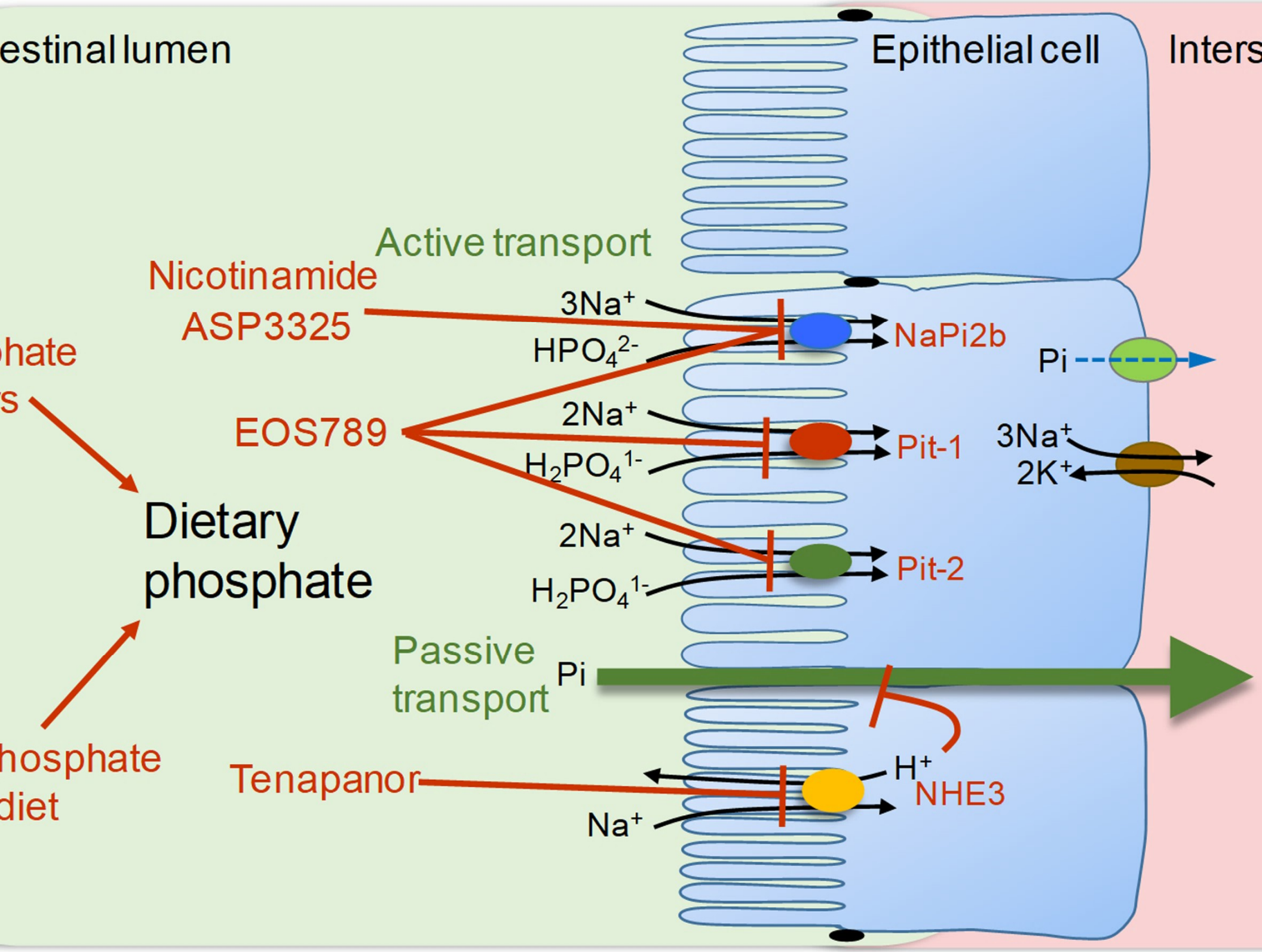
FIGURE LEGENDS

Figure 1. Different mechanisms of action of phosphate-lowering agents. Phosphate binders reduce the absorption of dietary phosphate in the intestine by forming a nonabsorbable compound in the lumen of the gastrointestinal tract that is excreted in the feces. Nicotinamide and ASP3325 inhibit sodium-dependent active intestinal phosphate absorption through the reduction of the intestinal NaPi2b phosphate transporter, whereas the pan-transporter inhibitor EOS789 targets both NaPi2b and the Pit1 and Pit2 transporters which are also localised in the intestine. Tenapanor reduces intestinal sodium and phosphate absorption by inhibiting the sodium/hydrogen ion-exchanger isoform 3 (NHE3), leading to intracellular proton accumulation and inducing a conformational change in tight junction proteins. This in turn decreases permeability to paracellular phosphate transport.

Box 1. Unmet needs/important questions to be addressed in hyperphosphatemia

No.	Unmet need/question
1	Long-term trials in larger patient cohorts are needed for nicotinamide and tenapanor. It is still unclear whether tenapanor can improve phosphate control compared to phosphate binders.
2	Information is also lacking as to whether tenapanor may also act synergistically when used in combination with phosphate binders.
7	The potential synergistic effect of tenapanor or nicotinamide with a phosphate binder remains to be fully understood and explored further in in-vivo studies and this has not been evaluated yet in CKD patients.
3	Long-term trials examining the effect of nicotinamide as add-on to phosphate binders are missing.
4	Novel mechanisms of action that have a pathophysiological rationale to address hyperphosphatemia are missing.
5	The mechanisms regulating phosphate control in healthy individuals is poorly understood, particularly how paracellular phosphate uptake occurs.
6	It is poorly understood as to why ASP3325 has been shown to be effective in preclinical studies but ineffective in patients.


estinal lumen
Epithelial cell
Inters
Active transport
Nicotinamide
ASP3325
3Na+
HPO4 2-
NaPi2b
Pi
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s
EOS789
2Na+
H2PO4 1-
Pit-1
3Na+
2K+
Dietary
phosphate
2Na+
H2PO4 1-
Pit-2
Passive
transport
Pi
hosphate
diet
Tenapanor
H+
NHE3
Na+